REMARKS

Claims 1-4, 6, 8, 9, 16, 18, 26-28 are pending.

Applicants note that independent claim 27, which stands rejected as obvious under 35 U.S.C. 103, is directed to a specific method of treating hyperlipidemia or hypercholesterolemia including administering the recited dosages of the claimed MTP inhibitor, and such methods offer surprising and unexpected advantages, as was discussed in the previous response and the previously submitted Declaration of William Sasiela, Ph.D. Because there is no mention of the substantial effort and evidence of this previous submission in the instant Action, such evidence does not appear to be considered by the Office. Applicants therefore respectfully request reconsideration and withdrawal of the final rejection of these claims.

Further, as the Action notes, claim 1 was amended to include some limitations of original claim 13, reciting the specific dosing of three claimed dosage levels. As is clear from the pending claims, the claimed invention is directed in part to the recited dosage levels of claim 1 or claim 27, which does not necessarily include a fifth dose level.

Claim Rejections under 35 U.S.C. § 102

Claims 1-4, 6, 8, 16 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Gregg et al., US 5,883,109. Applicants respectfully disagree with the Office analysis of this rejection on both a legal and factual basis.

Independent claim 1 recites a specific method that includes three step-wise, increasing dose levels of the MTP inhibitors wherein a first dose level is from about *2 to about 13 mg/day,* a second dose level is from about *5 to about 30mg/day*, and a third dose level is from about *10 to about 50 mg/day*. Nowhere in the Gregg et al. reference is there any teaching of such a method. Rather, Gregg et al., for example, teaches oral dose forms containing "5 to about 500 mg, preferably from about 10 to about 400 mg, and more preferably from about 20 to about 250 mg." Gregg et al. col. 23 ll. 17-19. As the Examiner knows, in order to anticipate claims, the claimed subject matter must be disclosed in the reference with "**sufficient specificity** to constitute an anticipation under the statute." M.P.E.P. 2131.03 (emphasis added). Applicant notes that the first dose level in recited in instant claim 1 includes a narrow range that in part falls out of the

scope of any disclosure of Gregg et al. Further, while Gregg et al. recite that compositions that may be administered "in single or divided doses of one to four times daily" there is no teaching of the specific claimed step-wise claimed dosages. Applicant notes that, while Gregg et al. states that it "may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination" such disclosure appears directed to a combination dose of HMG CoA reductase inhibitor, not to the recited MTP inhibitor of instant claim 1, and there is no teaching of the claimed step wise increase with the specific first, second and third dose levels of instant claimed 1.

Further, as the Action notes and is noted above, claim 1 was amended to include some limitations of original claim 13, reciting the specific dosing of three claimed dosage levels, which as noted above, are not taught by Gregg et al. Appicant notes that independent claim 27, reciting a specific first dose level and increasing second and third dose levels of the claimed MTP inhibitor, does not stand rejected under 35 U.S.C. 102. Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 9 and 26-28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gregg, U.S. Patent No. 6,057,339 ("Gregg") in view of Rosenblum et al. U.S5,767,115 ("Rosenblum"). Applicant respectfully traverses this rejection in view of the following comments.

The Action indicates that the "instant invention differs from the cited reference in the at the cited reference does not teach a fifth dose level" and that "one skilled in the art would have assumed that addition of a fifth administration is obvious since it is advisable to start a patient on a low dose and work up gradually to a high dose… in the **absence of evidence to the contrary**." (Emphasis added). As discussed above, and as is clear from the pending claims, the claimed invention is directed in part to the recited dosage levels of claim 1 or claim 27, which does not necessarily include a fifth dose level.

Applicant respectfully requests reconsideration of this rejection in light of consideration of all submitted evidence taken as a whole, including the previously submitted Declaration of

William Sasiela, Ph.D., In particular, as noted in the previous response and below, there is no teaching in Gregg et al. to select, without undue experimentation, the claimed low initial dose from the very broad range of disclosed dose levels –**a range that spans 1 to 2 orders of magnitude-**, and then a step-wise increase in dose levels, to arrive at the instantly claimed method that is both effective in significantly reducing adverse effects, and effective in treating hyperlipidemia or hypercholesterolemia.

Applicant submits that the standard of obviousness requires a consideration of whether the subject matter, taken as a whole, would have been obvious at the time the invention was made to a person skilled in the art. As the Examiner knows, combining prior art methods to reach a conclusion of obviousness requires: (i) a finding that the prior art included each element claimed, (ii) a finding that one of ordinary skill in the art could have combined the elements by known methods and that in combination each element merely would have performed the same function as it did separately; and (iii) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable.

Applicant notes that independent claim 27 recites a method that includes a specific dosing regimen. Neither Gregg nor Rosenblum teach an effective method that includes, for example, *initially administering a low dose of about 2 mg/day to about 13 mg/day, for about 1 to about 4 weeks*, and then an increasing second dose, and a third dose, as recited in claim 27. Rather, as noted above, Gregg teaches only oral dose forms containing "5 to about 500 mg, preferably from about 10 to about 400 mg, and more preferably from about 20 to about 250 mg."

Importantly, neither Gregg or Rosenblum recognize that the disclosed MTP inhibitor would cause **two** significant adverse effects, gastrointestinal related disorders *and* increase in hepatic fat, when administered to patients only at a *constant* level. As a consequence, previous phase II trials in human patients, initially administering 25 mg/day of the claimed compound, were discontinued because of such adverse events. (See e.g. instant specification at e.g., paragraph 115; Example 8, and the accompanying Declaration of William Sasiela Ph.D. (the "Declaration"). Further, neither the Gregg or Rosenblum recognize that the instantly claimed method would result in the reduced incidence of both of these adverse events, while still being efficacious. There is no guidance in Gregg to select, without undue experimentation, the claimed

low initial dose from the very broad range of disclosed dose levels –a range that spans 1 to 2 orders of magnitude-, and then a step-wise increase in dose levels, to arrive at the instantly claimed method effective in significantly reducing adverse effects.

For example, Applicants note that there is no reasonable expectation that one skilled in the art at the time of the instant invention would arrive at the claimed method. For example, the instant disclosure recognizes that the method provides for possible adaptation by the liver to the claimed MTP inhibitor once administered at a low dose level of the claimed MTP inhibitor, and such an initial low dose may continue to limit e.g. hepatic steatosis (fatty liver) even when the patient is ultimately administered a higher dose, as described in the instant specification for example, at page 26 paragraph 115. Further, as noted in the specification, it had been previously concluded, after a patient study using constant dose levels of 25 mg per day, (that the claimed MTP inhibitor *could not* be developed as a drug for large scale use in the treatment of hypercholesterolemia. (Specification, paragraph 33). The previously submitted Declaration indicates that others of skill in the art, including the scientists and investigators of the failed trial, did not appear to arrive at any solution these adverse events, and that the instant invention is non-obvious as to these prior art teachings.

Further, Applicants note, as described in the previously submitted Declaration, that the instantly claimed method, e.g. with an initial administration of about 5 mg/day for four weeks, and then step-wise increases to larger doses, results in *dramatic difference* in the rate of gastrointestinal (GI) effects as compared to a *constant* dose level administration of the claimed inhibitor- even when the constant dose level is substantially less than the dose administered after several step wise increases as instantly claimed. As noted in the Declaration, patients on a regimen such as described in claim 1 and 27 have a surprisingly lower rate of gastrointestinal adverse effects *even when ultimately administered up to 60 mg/day of the claimed MTP inhibitor as compared to patients administered a constant low level of 10 mg/day.* This significant reduction in GI effects is obtained even when patients also receive a further lipid modifying compound such as ezetimibe.

In contrast, Gregg appears to teaches starting low dose *combinations* of MTP inhibitors and other cholesterol lowering agents, effectively teaching away from the claimed method of the

low step wise dose levels of the MTP inhibitor and a constant level of another agent, e.g. ezetimibe.

Applicants submit that the standard of obviousness requires a consideration of whether the subject matter, *taken as a whole*, would have been obvious at the time the invention was made to a person skilled in the art. Without conceding any prima facie case of obviousness, Applicant believes that the Office must consider any rebuttal evidence, including showings that the claimed invention possesses superior properties, as described in the accompanying Declaration.

Applicant submits that the above references, either alone or in combination, fail to teach or suggest the claimed subject matter taken as a whole. In particular, the references alone or in combination, do not teach every limitation of the claims. Nor does the combination of each element of the claims merely perform the same function as it does separately. Further, there is no finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. Therefore, Applicant respectfully requests withdrawal of this rejection.

Any questions raised by this submission may be directed to the undersigned at (617) 570-8743. The Commissioner is hereby authorized to charge any underpayments, or credit any overpayments, to our Deposit Account No. 07-1700, **Reference: AGP-002**.

Respectfully submitted,

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